REMARKS

Upon entry of the present Amendment, claims 30 and 37-64 will be pending. Claims 1-29 and 31-36 are canceled. Applicant reserves the rights to pursue the withdrawn and/or canceled subject matter in a subsequent application.

Support for amended claims 30 and 57 for reciting "a neuregulin protein, consisting of an amino acid sequence set forth in SEQ ID NO:2" can be found throughout the application and, *inter alia*, at page 16, lines 23-26 of the present specification.

Support for new claim 59 can be found throughout the application and, *inter alia*, at page 4, lines 13-17, page 14, line 33 through page 15, line 2 and page 24, lines 2-5 of the present specification.

Support for new claims 60-62 can be found throughout the application and, *inter alia*, at page 15, lines 7-15 of the present specification.

Support for new claims 63 and 64 can be found throughout the application and, *inter alia*, at page 6, lines 33 through page 7, line 5 and page 23, lines 25-31 of the present specification.

The above-described amendments do not introduce any new matter into the present application.

Information Disclosure Statement

The Examiner states that the information disclosure statement filed 06/27/02 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because a number of references do not contain translations. In the Examiner's previous consideration of the IDS submitted on June 17, 2003 attached to the October 3, 2003 Office Action, the Examiner lined out references 11, 12, 15-17 and 19-21, for alleged lack of English translation of the references. Applicant responds as follows:

Reference No. 11 (EP 0,036,676): This reference is in English;

Reference No. 12 (EP 0,052,322): An abstract in English (Exhibit A) is submitted herewith;

Reference No. 15 (EP 0,102,324): The patent application in the same family, AU 1740283 A will be submitted subsequently. An abstract in English (Exhibit B) is submitted herewith;

Reference No. 16 (EP 0,133,988): The patent and patent application in the same family, AU 567572 B2 and AU 3139984 A will be submitted subsequently. The abstracts in English (Exhibit C and Exhibit D) are submitted herewith.;

Reference No. 17 (EP 0,142,641): Two patents in the same family, U.S. 4,590,060 A (Exhibit E) and U.S. 5,021,234 A (Exhibit F) are submitted herewith;

Reference No. 19 (EP 0,647,449): Two patent applications and two patents in the same family, U.S. 6,087,324 A (Exhibit G), U.S. 6,376,461 B1 (Exhibit H), US2002058622 A1 (Exhibit I) and US2002168337 A1 (Exhibit J), are submitted herewith;

Reference No. 20 (DE 3,218,121): An abstract in English (Exhibit K) is submitted herewith; and

Reference No. 21 (JP 83-118008): An abstract in English, published as JP 60007934 (Exhibit L), is submitted herewith.

Applicant respectfully submits that the submission of the English-language equivalent application/patent and the English language abstract of references 12, 15-17 and 19-21 complies with MPEP § 609.III.A(3) (An English-language equivalent application may be submitted to fulfill this requirement if it is, in fact, a translation of a foreign language application being listed in an information disclosure statement. There is no requirement for the translation to be verified. Submission of an English language abstract of a reference may fulfill the requirement for a concise explanation.) Accordingly, Applicant respectfully requests the Examiner to consider and make record of references 11, 12, 15-17 and 19-21 in the present application.

Election/Restrictions

Applicant appreciates the Examiner's acknowledgement of Applicant's election with traverse of Group II, claims 2, 16-17 and 25-29. Applicant reserves the rights to pursue the withdrawn and/or canceled subject matter in a subsequent application

Claim Rejections - 35 USC § 102

The Examiner states that the rejections of claims 30-31, 34 and 37-58 under 35 U.S.C. 102(b) as being anticipated by WO 94/26298 (Cambridge Neuroscience; Sklar et al.) and Balligand et al. (Jan./Feb.), 1997; 3(4):351-360), as well as the rejection of claims 2, 16-17, and 25-27 under 35 U.S.C. 102(e) as being anticipated by Sklar et al. (US 644642 Bl; Cambridge Neuroscience) and Gwynne et al. (US 6087323; Cambridge Neuroscience), are maintained for the reasons of record.

The Examiner states that Applicant argues that the references do not teach a method of using neuregulin to induce remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions, because the references do not expressly teach the underlying bio/physiological process that neuregulin is being administered in an amount sufficient to activate the MAP kinase pathway in cardiac muscle cells (and related cascade effects). The Examiner also states that Goldman et al. (US 6,162,641) and Reh et al. (US 6,750,196) are herein cited of record merely to indicate neuregulin's known intrinsic bio/physiological effect in cardiac cells.

Goldman et al. is alleged to teach neuregulin's effect through the MAP kinase pathway, in a method of using neuregulin in to treat muscle tissue, specifically cardiac muscle tissue (col. 7, lines 29-34), exogenously, that acts at a receptor on a cell [i.e. cardiac muscle cell] to cause a series of biochemical alterations in the MAP kinase signaling pathway/cascade within a cell [i.e. cardiac muscle cell] (col. 17, lines 38-42; Example 4, col. 33, lines 49-55). Reh et al. is alleged teach that neuregulins are membrane-anchored peptide growth factors that may mediate cell-cell interactions through cell-adhesion (col. 4, lines 17-23). The Examiner alleges that since the references teach the

use of neuregulin for cardiac muscle regeneration and related objectives, it is intrinsic that the underlying bio/physiological processes (i.e. cell-cell adhesion stimulation) achieving these objectives are carried out through an effective amount of neuregulin to activate the MAP kinase pathway.

Applicant respectfully traverses the rejection. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. As discussed in detail in the February 3, 2004 Amendment, WO 94/26298 and Balligand do not anticipate the presently claimed invention for a number of reasons. First, neither WO 94/26298 nor Balligand discloses or even mentions MAP kinase pathway in cardiac muscle cells at all; let alone any teaching of using neuregulin in an amount sufficient to activate the MAP kinase pathway in cardiac muscle cells. Indeed, WO 94/26298 teaches away from the presently claimed invention. As taught in the present specification:

> The higher ligand [neuregulin] concentration, concomitant with this increase in $p21^{CIPI}$ expression, resulted in a decrease in DNA synthesis, that was associated with terminal differentiation, whereas an increase in DNA synthesis and continued proliferation was observed with the lower dose (emphasis added).

(*See* page 6, lines 33 through page 7, line 5 of the present specification). In contrast, WO 94/26298 teaches the use of neuregulin at an amount that induces mitogenesis, and hence DNA synthesis. (*See* February 3, 2004 Amendment at pages 18-19.)

Neither Goldman nor Reh cures the defects of WO 94/26298 or Balligand. Goldman "relates to a nucleic acid comprising an neuregulin response element (NRE) and its therapeutic applications and uses in methods for drug screening." (Goldman at col. 2:16-18.) Goldman is irrelevant to the present invention, the use of an neuregulin protein of inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions, or treating or delaying disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures in a mammal.

The specific passages relied upon by the Examiner is also irrelevant to the present invention. For example, the Examiner cited col. 7, lines 29-34, apparently for a teaching of a method of using neuregulin to treat muscle tissue, specifically cardiac muscle tissue. The Examiner's reliance on this passage is erroneous. Goldman states:

> One aspect of the present invention provides a method for obtaining expression at a neuromuscular junction (NMJ) of a protein encoded by a gene, in a cell of a subject in need of the protein, comprising contacting a cell of that subject with a nucleic acid comprising at least the gene encoding the protein, operably linked to nucleic acid comprising the neuregulin-PTPase-Ras sensitive nAChR €-subunit regulatory element, to produce a genetically transformed cell, which expresses the protein encoded by the gene at the NMJ. In one embodiment, the method can include a step in which the cell is contacted in the subject in vivo. In this embodiment, it is preferably that the cell is in muscle tissue, or is a nerve cell.

(Goldman at col. 7:21-34.) It is clear that the method discussed in this passage has nothing to with treating anything, including the cell in muscle tissue relied upon by the Examiner, with an neuregulin protein.

The Examiner also cited col. 17, lines 38-42 of Goldman, where it is stated the "agent can be supplied exogenously, for example, exogenously supplied neuregulin that is added to the culture medium and that acts at a receptor on a cell to cause a series of biochemical alteration in the MAP kinase signaling pathway within a cell." The Examiner further cited Example 4, col. 33, lines 49-55 of Goldman for a similar statement. The passages cited by the Examiner, at most, states that neuregulin can activate a MAP kinase signaling pathway within a cell. Goldman, whether in general or in the specific passages cited by the Examiner, does not disclose the present invention, the use of an neuregulin protein to activate a MAP kinase signaling pathway for inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions, or for treating or delaying disassociation of cardiac muscle cell-cell adhesion and/or the disarray of

sarcomeric structures in a mammal. It is the present applicant who discovered that an neuregulin protein must be used in an amount sufficient to activate the MAP kinase pathway in cardiac muscle cells or tissues to achieve the intended benefit. Merely stating that an neuregulin protein can be used on cardiac muscle cell, as in Balligand; or that an neuregulin protein can be used on cardiac muscle cell in an amount not sufficient to activate the MAP kinase pathway, as in WO 94/26298; or that an neuregulin protein can be used to activate the MAP kinase pathway in a cell generally, as in Goldman, does not anticipate the present invention.

Reh is directed to "methods for promoting the function of retinal cells using neuregulins." (Reh col. 6:3-4.) Like Goldman, Reh is irrelevant to the present invention, the use of an neuregulin protein of inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions, or treating or delaying disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures in a mammal. The Examiner cited col. 4, lines 17-23 of Reh, where it is stated:

> Although a large number of neuregulins may be produced by alternative splicing, they can be broadly sorted into the putative membrane-bound and the soluble isoforms. The former contains a putative trans-membrane domain and may be presented at the cell surface. Membrane-anchored peptide growth factors may mediate cell-cell interactions through cell-adhesion or juxtacrine mechanisms (reviewed by Massague and Pandiella, Ann. Rev. Biochem. 62:515, 1993).

It is clear that the cited passage simple states that the membrane-anchored neuregulin may mediate cell-cell interactions through cell-adhesion or juxtacrine mechanisms generally. Such a generalized statement is irrelevant to the present invention, which is specifically directed to the use of neuregulin activate a MAP kinase signaling pathway for inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions, or for treating or delaying disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures in a

mammal. In the same passage cited by the Examiner, Reh states that "neuregulins may function as injury factors." (Reh col. 4:34-35.) This can hardly be a teaching of the present invention, which in some aspect is directed to the use of neuregulin to treat heart failures.

In addition, WO 94/26298, at most, discloses the use of neuregulin to enhance muscle cell proliferation and differentiation.. Similarly, Balligand, at most, discloses the use of neuregulin in cardiac endothelium and tissue growth, and specifically regulation of cardiac myocyte growth. According to the Examiner's own restriction requirement, which is made final here, a method of causing cardiomyocyte growth and/or differentiation using neuregulin (Group I) is patentably distinct from a method of inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures, or cell-cell adhesions using neuregulin (Group II). The Examiner did not address this argument at all in the Final Office Action.

Moreover, to advance prosecution of the present application, claims 30 and 57 are amended to recite "a neuregulin protein, consisting of an amino acid sequence set forth in SEQ ID NO:2." None of the cited references discloses the use of the recited neuregulin protein.

Further, both claims 46 and 64 require "sustained activation of the MAP kinase pathway in the cardiac muscle cells." As shown in the present specification:

> NRG function through two distinct pathways: one activated at lower ligand concentrations results in cardiomyocyte growth, whereas the other, activated with higher concentrations, is mediated by sustained activation of the MAP kinase pathway and results in terminal differentiation and maturation

(The present specification at page 7, lines 19-23.) None of the cited references, including WO 94/26298, Balligand, Goldman and Reh, discloses treating cardiac muscle cells at a sufficiently high concentration to achieve sustained activation of the MAP kinase pathway in the cardiac muscle cells. Therefore, none of the cited references anticipates claims 46 and 64 for this additional reason.

It is respectfully submitted that the rejections of claims 30-31, 34 and 37-58 under 35 U.S.C. § 102 are overcome by the above remarks and/or amendments and must be withdrawn.

Rejection under 35 U.S.C. §103

The Examiner states that the rejection of claims 30-31, 34, and 37-58 under 35 U.S.C. 103(a) as being unpatentable over any of WO 94/26298 (Cambridge Neuroscience; Sklar et al.), Sklar et al. (US 644642 B1; Cambridge Neuroscience), Gwynne et al. (US 6087323; Cambridge Neuroscience), or Balligand et al. (Jan./Feb.), 1997; 3(4):351-360), is maintained for the reasons of record. The Examiner also states that Applicant's arguments have been fully considered, but are not found persuasive (see the discussion above, as also applicable in it's entirety to the rejections under 35 U.S.C. § 103).

This rejection is respectfully traversed. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. As discussed above in connection with the anticipation rejection, nowhere does any of the cited references teach or suggest the use of neuregulin, generally or a neuregulin protein consisting of an amino acid sequence set forth in SEQ ID NO:2, in an amount sufficient to activate the MAP kinase pathway in cardiac muscle cells. Similarly, nowhere does any of the cited references teach or suggest the use of neuregulin, generally or a neuregulin protein consisting of an amino acid sequence set forth in SEQ ID NO:2, to induce remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions of cardiac muscle cells or to treat or delay disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures.

It is respectfully submitted that the rejection of claims 30-31, 34, and 37-58 under 35 U.S.C. § 103 is overcome by the above remarks and/or amendments and must be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 524012000200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: May 23, 2003

Respectfully submitted,

By _____

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Method of preparing lipid vesicles by ultrasonic treatment, the use of this method and apparatus for its application

Patent number: EP0052322
Publication date: 1982-05-26
Inventor: GERSONDE KLAUS PROF DR MED; SCHAL WILFRIED DR
Applicant: GERSONDE KLAUS PROF DR (DE)
Classification:
- international: A61K9/50
- european: A61K9/127P; A61K9/50H8B
Application number: EP19810109575 19811109
Priority number(s): DE19803042360 19801110

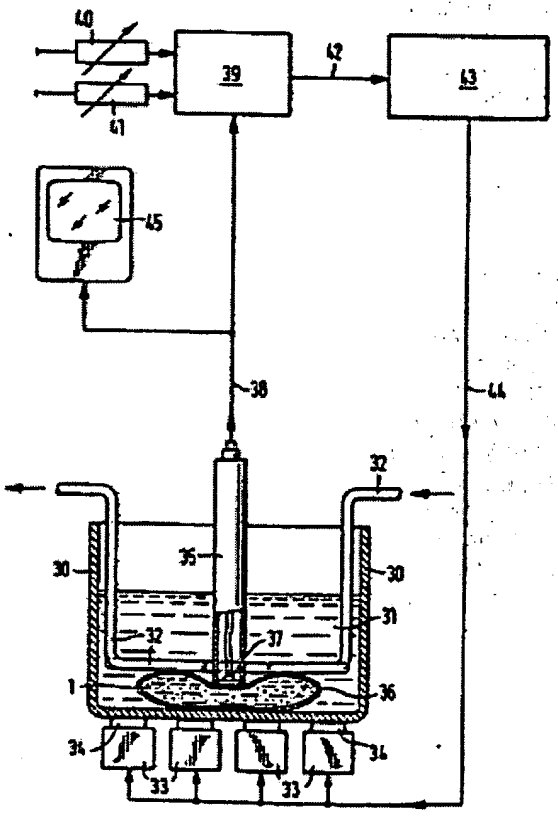
Also published as:
EP0052322 (A3)
EP0052322 (B1)

Cited documents:
DE2338503

Abstract of **EP0052322**

1. A method of preparing lipid vesicles from biological membranes or lipid suspensions, in which the lipid suspensions or lipid particles to be desintegrated are ultrasonically treated in a dispersion fluid inside a treatment container at a substantially constant temperature, characterized in that the size respectively size distribution of the lipid vesicles, effective for the desired purpose, and the optimum ultrasonic frequency and intensity in the dispersion fluid required for obtaining this size respectively this size distribution are determined, and that the thus determined optimum ultrasonic frequency and intensity, with the other constant conditions, are maintained constant in such a manner that during the ultrasonic treatment the actuel value of frequency and intensity of the ultrasonic field in the reaction medium is continuously measured and the output power and the frequency of the electric generator supplying the sound transmitter are controlled in dependence upon the actuel value of the frequency and intensity of the ultrasonic field.

Fig. 2



LIPIDS AND TENSIDS IN AQUEOUS PHASE

Patent number: AU1740283
Publication date: 1984-02-02
Inventor: HAUSER HELMUT
Applicant: CIBA GEIGY AG
Classification:
- international: A61K9/10; C07G17/00
- european: A61K9/127B2
Application number: AU19830017402D 19830728
Priority number(s): CH19820004597 19820729

Also published as:
EP0102324 (A2)
JP59089633 (A)
ES8602434 (A)
EP0102324 (A3)
DK346183 (L)

Abstract not available for AU1740283
Abstract of corresponding document: **EP0102324**

The present invention relates to an advantageous process for preparing unilamellar liposomes in aqueous phase by dispersing a homogeneous mixture of an ionic surfactant and of a lipid. The unilamellar liposomes are formed spontaneously, i.e. without input of additional external energy. The liposomes obtained by the process can be used as carriers of a wide variety of active substances for therapy.

PHARMACEUTICAL PRODUCTS WITH PROTRACTED RELEASE WHICH CONTAIN REGULATORY PEPTIDES

Patent number: AU567572
Publication date: 1987-11-26
Inventor:
Applicant: HOECHST AG
Classification:
- international: A61K37/02; A61K47/00
- european: A61K9/00M4; A61K9/20H6D4; A61K38/16
Application number: AU19840031399 19840801
Priority number(s): DE19833327856 19830802; DE19833336197 19831005

Also published as:
EP0133988 (A2)
ES8504455 (A)
PT79007 (B)
GR82450 (B)
DK373584 (L)

Abstract not available for AU567572
Abstract of corresponding document: **EP0133988**

Implants containing regulatory peptides or their analogues as active ingredients and natural poly-D-(-)-3-hydroxybutyric acid as biodegradable vehicle, and process for their preparation, are described. The active ingredient undergoes protracted release from the implants.

Serial No. 09/980,672

PHARMACEUTICAL PRODUCTS WITH PROTRACTED RELEASE WHICH CONTAIN REGULATORY PEPTIDES

Patent number: AU3139984
Publication date: 1986-09-11
Inventor:
Applicant: HOECHST AG
Classification:
- international: A61K37/02; A61K47/00
- european: A61K9/00M4; A61K9/20H6D4; A61K38/16
Application number: AU19840031399D 19840801
Priority number(s): DE19833327856 19830802; DE19833336197 19831005

Also published as:
EP0133988 (A2)
ES8504455 (A)
PT79007 (B)
GR82450 (B)
DK373584 (L)

Report a data error here

Abstract not available for AU3139984
Abstract of corresponding document: **EP0133988**

Implants containing regulatory peptides or their analogues as active ingredients and natural poly-D-(-)-3-hydroxybutyric acid as biodegradable vehicle, and process for their preparation, are described. The active ingredient undergoes protracted release from the implants.

PREPARATION OF LIPOSOME

Patent number:	JP60007934
Publication date:	1985-01-16
Inventor:	HIROTA SADAO; KIKUCHI HIROSHI
Applicant:	DAIICHI SEIYAKU CO
Classification:	
- international:	A61K31/60
- european:	A61K9/127P
Application number:	JP19830118008 19830629
Priority number(s):	JP19830118008 19830629

Abstract of **JP60007934**

PURPOSE:To prepare uniform liposome efficiently and in large amt. by hydrating liposome membrane composing substance by kneading it with a small amt. of aq. solvent at a temp. above the phase transfer temp. of the membrane composing substance. CONSTITUTION:1pt.wt. liposome membrane composing substance (e.g. phosphatidyl choline) is hydrated by kneading it with ca.0.2-8pts.wt. aq. soln. (e.g. water) at a temp. above the phase transfer temp. of the membrane composing substance. Then, necessary amt. (10-1,000pts.wt.) of aq. soln. is added to the mixture, and obtd. mixture is stirred at a temp. above the phase transfer temp. of the membrane composing substance. As a result, uniform liposome is obtd. efficiently and in a large amt.